THIOESTERS AND THE RNA WORLD

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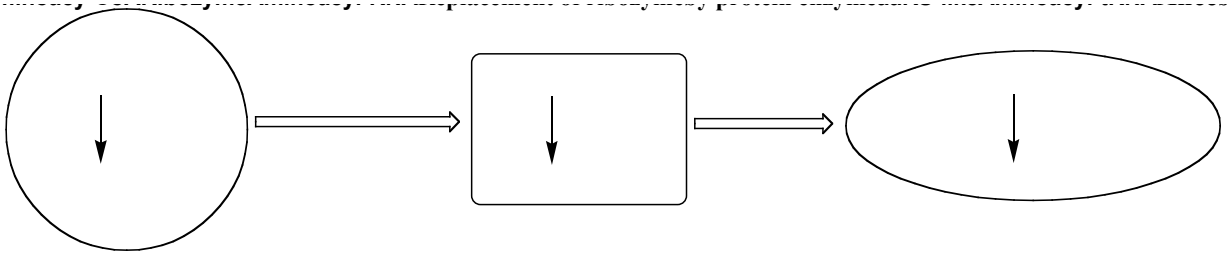
A thioester bond represents an optimal balance between a "high energy" bond and its sufficient hydrolytic stability. Therefore, contemporary biology uses thioesters (such as acetyl CoA) extensively as the activated intermediates in a variety of transacylation reactions, including fatty acid biosynthesis, acylglycerol synthesis, citric acid synthesis in the citric acid cycle, and biosynthesis of amino acids. In addition, polyketide synthases (PKS) and nonribosomal polypeptide synthetases (NRPK) empoy thioesters of fatty acids and amino acids as the key intermediates to build bioactive polyketides and peptides. It has been suggested that the importance of thioesters could have been placed back to the early stages of evolution, e.g., the RNA world.

Using RNA as the catalyst, we have demonstrated that a variety of thioesters can be synthesized efficiently (1). In addition, we have shown that a simple molecule imidazole is an excellent catalyst for the synthesis of thioesters in aqueous solutions, yields ≥ 90% thioesters within 10 min at room temperature at millimolar and sub-millimolar substrate concentrations (2). These experiments have therefore demonstrated the plausible availability of thioesters in the RNA world by different mechanisms.

To demonstrate the utility of thioesters as activated intermediates for the construction of biomolecules, we have isolated ribozymes that catalyze the synthesis of aminoacylated RNA (similar to amino acid-charged tRNA) using aminoacyl CoA thioesters as substrates (3). The results, in combination with the chemistry of PKS and NRPK, as well as the functions of acyl carrier proteins, have led us to propose that current aminoacyl tRNA synthetases (aaRS) could have evolved from aminoacyl CoA-utilizing ribozyme systems. As the supporting evidence, many of aaRS's contain a nonfunctional thiol binding site. This nonfunctional thiol binding site could have been a molecular vestige from an ancestral ribozyme system that had possessed an aminoacyl CoA binding site.



1. Coleman, T. M., and Huang, F. (2002) RNA-catalyzed thioester synthesis. *Chem. Biol.* **9,** 1227-1236.

2. Coleman, T. M., Li, N., and Huang, F. (2005) A simple and efficient method to prepare thioesters in aqueous solutions. *Tetrahedron Lett.* **46,** 4307-4310.

3. Li, N., and Huang, F. (2005) Ribozyme-catalyzed aminoacylation from CoA thioesters. *Biochemistry* **44,** 4582-4590.